Latency Period of Thyroid Neoplasia After Radiation Exposure

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Objective: To determine the temporal sequence for developing benign and malignant thyroid neoplasms after radiation.

Summary Background Data: Therapeutic radiation is associated with thyroid neoplasms in humans and animals. Some question whether thyroid cancers develop de novo or from benign thyroid neoplasms. Little information, however, is available concerning the time to development of benign and malignant thyroid neoplasms after radiation exposure.

Methods: We retrospectively analyzed the records of 171 consecutive patients who had a history of exposure to radiation and were treated surgically at University of California, San Francisco-affiliated hospitals for thyroid neoplasms between 1960 and 1999.

Results: There were 66 men and 105 women aged 9 to 80 years (mean, 47.0 years). One hundred patients had benign and 71 had malignant tumors (58 papillary cancers, 10 follicular cancers, 1 Hurthle cell cancer, 1 medullary cancer, and 1 carcinosarcoma). The mean latency period for benign tumors was longer than that for malignant lesions (mean, 34.1 and 28.4 years, $P = 0.018$; median, 38.0 years and 30.0 years, $P = 0.001$). Follicular carcinomas developed sooner (mean, 20.5 years; median, 20 years) than did follicular adenomas (mean, 35.3 years; median, 36.5 years; $P = 0.003$, $P = 0.0009$). Patients with papillary thyroid cancers presenting as occult papillary cancers (<1 cm) and as a dominant nodule had similar latency periods (mean, 34.0 and 28.0 years $P = 0.29$; median, 37.5 and 30.5 years, $P = 0.09$), respectively.

Conclusion: Although there could be selection bias regarding referral of patients, our data document that malignant thyroid tumors after radiation exposure, including follicular carcinomas, present earlier than do benign thyroid tumors. Occult and manifest papillary thyroid cancers present at about the same time interval after radiation exposure. Our findings question whether benign thyroid neoplasms progress to malignant thyroid neoplasms and that most occult thyroid cancers do not progress to malignant thyroid cancers in radiation-exposed patients.

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Ionizing radiation is a well-established risk factor for the development of benign and malignant thyroid neoplasms.[1] Knowledge about radiation-induced thyroid neoplasms comes largely from studies of children exposed to radiation of the head and neck for benign disease as well as studies of individuals exposed to nuclear fallout from atomic bomb detonations[2] and the Chernobyl nuclear power plant accident.[3] In the past, patients (primarily children) were irradiated for enlarged thymus, tonsils and adenoids, cervical lymphadenopathy from tuberculosis, cerebral tumors and benign skin conditions, including keloids, acne, birthmarks, and tinea capitis. Thousands of children were irradiated in the United States and other countries between the years 1920 to 1950. Approximate dosages ranged from 6 to 1500 rads.[4] Although the administration of low dose therapeutic radiation for benign conditions is no longer performed, radiation is still used to treat patients with Hodgkin's disease, lymphomas, squamous cell carcinomas, and other tumors. Persons have also been exposed to radiation from fallout as a result of atomic bomb explosions and nuclear plant accidents. Patients are also currently being treated with radioiodine for Graves' disease, toxic nodular goiter, and other conditions.[2,3]

Several models of thyroid carcinogenesis based on the Vogelstein's model of colon cancer have been proposed by Wynford-Thomas et al[5] and Fagin et al[6] These models suggest that papillary and follicular cancers are associated with different oncogenes, as are "hot" and "cold" follicular neoplasms. Many investigators believe that there is a step-wise progression from benign to malignant disease for follicular neoplasms and that most clinically evident papillary thyroid cancers began as occult papillary cancers. Evidence also suggests that most undifferentiated thyroid cancers arise from differentiated thyroid cancers.[7] More information must be

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gained to support or refute these theories. The development of thyroid cancers after radiation exposure may also differ from thyroid cancers that develop spontaneously. In the former, one can document the time between radiation exposure and the subsequent diagnosis and treatment of the thyroid nodule or nodules.

The purpose of this retrospective investigation was to analyze the time or latency period from radiation exposure until the clinical diagnosis of a thyroid neoplasm. We also analyzed whether the age of the patient or the approximate dose of radiation received influenced the latency period or the type of thyroid neoplasms that developed.[3] Our investigation suggests that the time from radiation to the development of thyroid neoplasms does not support the commonly proposed belief that there is progression from benign to malignant thyroid neoplasms in patients previously exposed to low dose radiation.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the records of 171 consecutive patients who underwent thyroid operations for thyroid neoplasms between the years 1960 and 1999 at University of California San Francisco (UCSF)-affiliated medical centers (UCSF, UCSF/Mount Zion, and Veterans Affairs Medical Centers) and had a prior history of external radiation to either head or neck, or received internal radiation from treatment with radio iodine, or from environmental radiation exposure. All diagnoses were confirmed histologically. All patients in whom records were available were included. Patients with exposure to radiation after thyroid operations such as for scanning or therapy with radioiodine were excluded. The time from radiation to thyroid operation was determined and analyzed by patient age at treatment, gender, physical examination, source and dosage of radiation, date of exposure, and age at exposure.

Estimated Dosage of Radiation

We divided the estimated dosage of radiation into a low dose therapeutic radiation group (<2000 rads), a medium dose group (2000 to 4000 rads) and a high dose group (>4000 rads). Low-dose radiation was used for treating enlarged thymus, tonsils and adenoids, cervical lymphadenopathy from tuberculosis, external otitis, and benign skin conditions, including keloids, birthmarks, acne, and tinea capitis. Medium-dose irradiation was used primarily for patients with Hodgkin's and non-Hodgkin's lymphoma. High-dose irradiation was used to treat malignant head and neck tumors and radioiodine for patients with Graves' disease, toxic nodular goiter, and in patients exposed to radiation fallout from the Chernobyl nuclear accident in 1986.[8] Overall 152 patients received external radiation and 19 radioactive iodine or lived near Chernobyl at the time of the nuclear plant accident. The estimated age at the time of radiation exposure and latency period were determined by documenting age when exposed to radiation and age at the time of histologic diagnosis. Tumor size and tumor aggressiveness of benign or malignant thyroid tumors were determined from the pathology and operative reports. We estimated tumor aggressiveness using the DeGroot classification.[9]

Results are expressed as the mean and standard deviations. Statistical analysis was performed using Statview (Statview, Cary, NC). Two-group comparisons were analyzed by unpaired t tests. Values of $P < 0.05$ were considered to be statistically significant.

RESULTS

There were 105 women and 66 men with a mean age of 46.1 years for women and 49.1 years for men at the time of thyroidectomy. Patient ages at time of exposure ranged from 1 day to 72 years. Most patients (137/171 = 80%) were younger than 21 years when exposed. Seventy-one patients developed malignant thyroid tumors (58 papillary carcinoma, 10 follicular carcinoma, 1 medullary carcinoma, 1 Hürthle cell carcinoma, and 1 carcinosarcoma) and 100 patients developed benign neoplasms (69 multinodular goiters, 24 follicular adenomas, 6 Hürthle cell adenomas, 1 histiocytoma). Most 127/171 (74%) patients were treated by total thyroidectomy, 22 (13%) by completion total thyroidectomy, and 22 (13%) by lesser operations. All patients were exposed to radiation between 1920 and 1996. The pertinent clinical information is listed in Tables 1 and 2.

Latency Period of Benign and Malignant Thyroid Tumors

Although some sporadic tumors unrelated to radiation may be included among our patients, the shortest latency period for both benign and malignant tumors was 1 year as occurred in 3 patients, whereas the longest time was 69 and 58 years, respectively (Fig. 1). The number of benign and malignant neoplasms tended to increase for the first 4 decades after radiation exposure. Benign and malignant tumors, however, continued to be diagnosed up to 6 and 5 decades, respectively, after radiation exposure. Fifty-four percent (93/171) of all patients developed thyroid neoplasms between 30 and 50 years after radiation exposure. The mean time till the clinical development of benign and malignant tumors was 34.1 and 28.5 years respectively (median time was 38.0 years and 30.0 years, respectively). There was a significant difference between the time till development of benign and malignant neoplasms ($P = 0.018$). Among those with malignant tumors, thirty-four out of 71 (48%) had coexisting benign nodules and 6 out of 71 (8%) had evidence of thyroiditis.

TABLE 1. Thyroid Neoplasms After Radiation Exposure (171 Patients)

	No.	Tumors	No.		No.
Gender		*Benign*	100	*Malignant*	71
Female	105	Multinodular goiter	69	Papillary carcinoma	58
Male	66	Follicular adenoma	24	Occult*	21
Age (mean ± SD)		Hürthle cell adenoma	6	Manifest	35
Female	46.1 ± 13.6	Histiocytoma	1	Follicular carcinoma	10
Male	49.1 ± 13.7			Hürthle cell carcinoma	1
Total	47.0 ± 14.0			Medullary carcinoma	1
				Carcinosarcoma	1
				Unknown	2

*Occult < 1.0 cm.

TABLE 2. Surgical Procedure and Pathology

		Pathology			
Operation	**No.**	**Coexisting Neoplasms**	**No.**	**DeGroot Classification**	**No.**
Total thyroidectomy	127	Malignant + benign tumor	34	I (within thyroid)	43
Less than ttx then completion	22	Malignant + thyroiditis	6	II (nodal involvement)	13
Less than ttx only	22			III (local invasion)	8
				IV (distant metastasis)	3
				unknown	4

ttx, total thyroidectomy.

Latency Period of Follicular and Hürthle Cell Neoplasms

Forty-one patients were diagnosed with follicular (n = 34) or Hürthle cell (n = 7) neoplasms (Fig. 2). The year of exposure ranged from 1920 to 1989, mean decade was 1956. Seventy-six percent (31/41) of patients were younger than 21 years of age at time of exposure with a mean age of 14.5 years. Mean and median latency periods from the time of radiation exposure till the diagnosis of combined benign follicular and Hürthle cell tumors was 35.3 and 36.5 years and mean and median latency periods for combined malignant follicular and Hürthle cell tumors was 20.5 and 20 years, respectively. There was a significant difference between these 2 groups ($P < 0.01$). Most patients (22/30 = 73%) with follicular adenomas or Hürthle cell adenomas had a latency period of between 20 and 50 years (mean 36.2 years, median 36.5 years), whereas most patients (10/11=91%) with follicular carcinomas or Hürthle cell carcinomas had a latency period of from 10 to 40 years (mean 22.8 years, median 21.5 years). There were no differences in latency periods for the development of follicular and Hürthle cell neoplasms (mean values 31.1 year versus 33.3 years, $P = 0.7$, median values 34.0 years versus 30.0 years, $P = 0.5$).

Latency Period of Occult and Dominant Papillary Cancers

Fifty-eight patients were diagnosed with papillary thyroid cancer (Fig. 3). The year of exposure ranged from 1930–1995. Seventy-eight percent (45/58) of patients were younger than 21 years of age at time of exposure with a mean age of 16.4 years. The mean and median latency period of papillary thyroid cancer was 30.1, 31.5 years, respectively. Thirty-three percent (19/58) of patients had a latency period of between 30 and 40 years. There was no difference between patient age at exposure and presentation of dominant or occult papillary thyroid carcinoma. The mean and median latency of occult papillary carcinoma (maximal diameter < 1.0 cm) were 34.0 and 37.5 years, and mean and median latency of clinically manifest papillary carcinomas were 28.0 and 30.5 years. There was no significant difference between these 2 groups ($P = 0.29$, $P = 0.09$).

Correlation Between the Latency Period and Dosage of External Radiation

One hundred and fifty-two patients were exposed to external radiation (Fig. 4). Most (121/132 = 92%) of the patients were younger than 21 at the time of exposure,

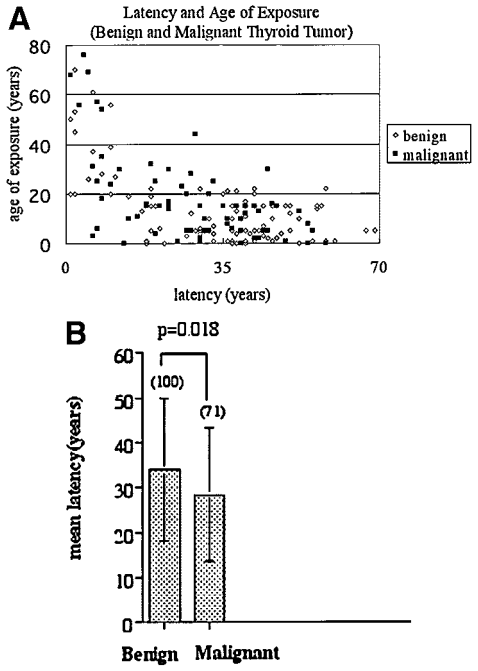

FIGURE 1. Latency and age of exposure in benign and malignant thyroid neoplasms. A, White diamonds show benign thyroid tumors and black squares show malignant tumors. B, Each histogram represents the mean ± SD. There is no difference between mean and median. The patient's number was shown in the parenthesis. Latency of benign thyroid tumors is longer than that of malignant thyroid tumors ($P = 0.018$).

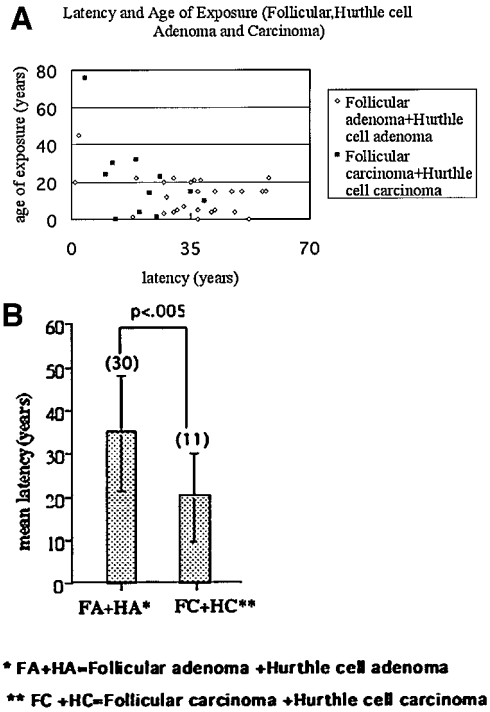

FIGURE 2. Latency and age of exposure in follicular and Hürthle cell neoplasms. A, White diamonds show follicular and Hurthle cell adenomas and black squares show follicular and Hürthle cell carcinomas. B, Each histogram represents the mean ± SD. There is no difference between mean and median. The patient's number was shown in the parenthesis. FA; follicular adenoma, FC; follicular carcinoma. HA: Hürthle cell adenoma, HC: Hürthle cell carcinoma. Latency of malignant & Hurthle cell cancer is shorter than that of benign tumors.

whereas 50% (10/20) patients exposed to medium and high dose radiation were older than 21.

There appeared to be no direct correlation between the time to development of thyroid neoplasms and dosage of external radiation. When patients were separated into those exposed to low-dose radiation (less than 2000 rads), those exposed to medium-dose radiation (2000 rads to 4000 rads), and those exposed to high-dose radiation (more than 4000 rads), the mean and median latency periods till tumor removal was 37.0, 14.9, and 15.0 years and 38.0, 12.0, 7.5 years, respectively. In patients receiving low-dose radiation, benign tumors were documented at mean 39.1 year (median 40.0 years) and malignant tumors at mean 33.6 years (median 34.0 years; $P = 0.01$). Occult papillary thyroid cancers were removed at mean 35.9 years (median 38.5 years), and manifest papillary thyroid cancers at mean 34.4 years (median 32.5 years; $P = 0.68$). Surprisingly follicular and Hürthle cell adenomas were removed at mean 39.7 years (median 37.0 years) after radiation exposure and follicular and Hürthle cell carcinomas mean 26.1 year (median 25.0 years) after radiation exposure ($P = 0.001$). In patients exposed to 2000 to 4000 rads, the mean and median latency periods till the identification of benign tumors was 9.6 and 8.0 years and for malignant tumors 27.8 and 28.0 years respectively ($P = 0.01$). In patients receiving more than 4000 rads, benign tumors were noted at mean 14.8 years (median 17.0 years) and malignant tumors at mean15.2 years (median 7.0 years) ($P = 0.97$).

Internal Radiation

Nineteen patients were exposed to internal radiation, among them thirteen patients received radioiodine and 6 patients were exposed to radiation fallout due to the Chernobyl nuclear plant accident. After exposure to radioiodine, there was also no significant difference between the mean and median latency periods or till surgical treatment of benign (16.5 years, 8 years) and malignant (10.0 years, 8 years) thyroid tumors, respectively ($P = 0.35$). Among the 6 patients who were exposed to radiation during the Chernobyl nuclear accident, 2 had benign and 4 had malignant thyroid tumors (3 papillary thyroid carcinoma, 1 follicular carcinoma). The mean and median latency periods till treatment of benign thyroid tumors were 8 years and 8 years, and for

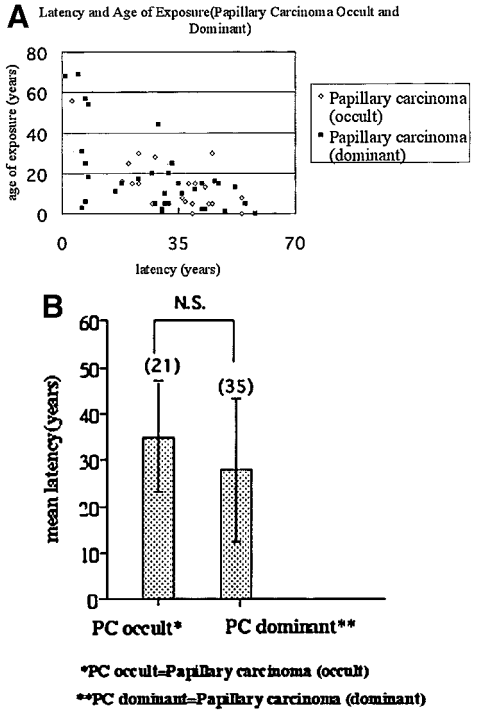

FIGURE 3. Latency and age of exposure in occult and dominant papillary thyroid carcinomas. A, White diamonds show occult papillary thyroid carcinomas and black squares show dominant papillary thyroid carcinomas. B, Each histogram represents the mean ± SD. There is no difference between mean and median. The patient's number was shown in the parenthesis. Two patients are unknown because they had surgery at other medical centers. PC oc; occult papillary carcinoma, PC dominant; dominant papillary carcinoma. Latency of dominant or manifest papillary thyroid cancers is the same as that of occult papillary cancers ($P = 0.29$).

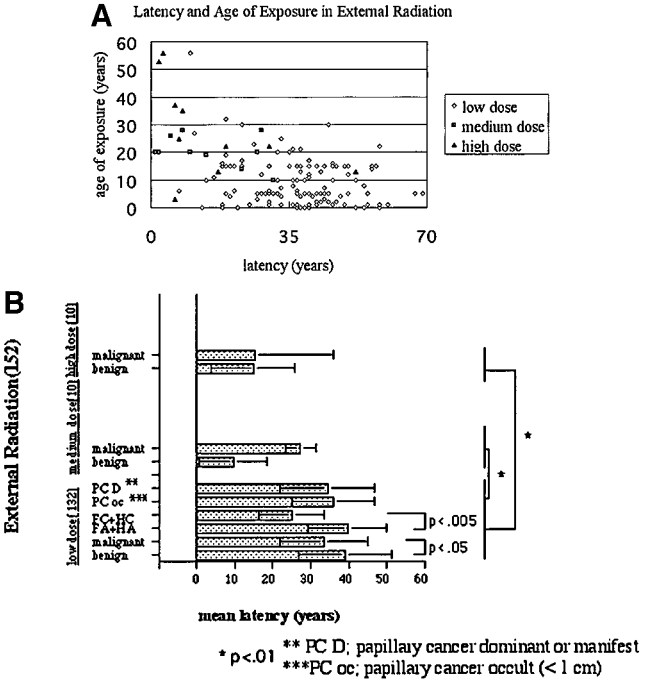

FIGURE 4. Latency and age of exposure in external radiation. One hundred and fifty-two patients were exposed external radiation. A, White diamonds show low dose exposure, gray squares show medium dose exposure and black triangle show high dose exposure. Low dose is below 2000 rads, medium dose is between 2000 rads and 4000 rads, and high dose is higher than 4000 rads. B, Each histogram represents the mean ± SD. There is no difference between mean and median. Latency of low dose radiation exposure is longer than that of medium and high dose radiation exposure ($P < 0.01$). In the subgroup of low dose radiation exposure, latency of benign thyroid tumors is longer than that of malignant thyroid tumors ($P = 0.01$) and latency of malignant follicular tumors is shorter than that of benign follicular tumors ($P = 0.001$).

thyroid cancers 7.8 years and 7 years, respectively. For papillary thyroid carcinomas, it was 6.3 years and 6 years. This latency period was similar to the time that occurred in patients exposed to high dose external radiation from causes other than Chernobyl (15.0 years), but significantly different ($P < 0.05$) from the latency period in patients exposed to low dose radiation from other sources.

Latency Period, Tumor Size, and Tumor Aggressiveness

There was no correlation between the latency period before patient tumors were treated and tumor size for either benign or malignant thyroid tumors (R = 0.23, $P = 0.22$, R = −0.18, $P = 0.14$; Fig. 5). There was also no difference between the latency period for occult (< 1cm) and manifest thyroid cancers. There was also no correlation between the latency period and the stage of the malignant thyroid cancer when compared by the DeGroot classifications (Pearson's correlation R = 0.117, $P = 0.35$).

DISCUSSION

Our data surprisingly document that malignant thyroid tumors of follicular cell origin including follicular carcinomas become clinically evident either before or at the same time as benign thyroid tumors after radiation exposure. Occult and manifest papillary thyroid cancers also present at about the same time interval after radiation exposures. There was no correlation between the tumor size or tumor stage and latency period. Although there could be bias in our investigation since patients with benign thyroid tumors might be followed longer before referral, our studies do not support the hypothesis of gradual progression from benign to malignant tumors, from occult to manifest papillary carcinomas, or from follicular or Hürthle cell adenomas to follicular or Hürthle cell carcinomas. The knowledge that thyroid nodules, in patients with a history of radiation exposure, are more likely

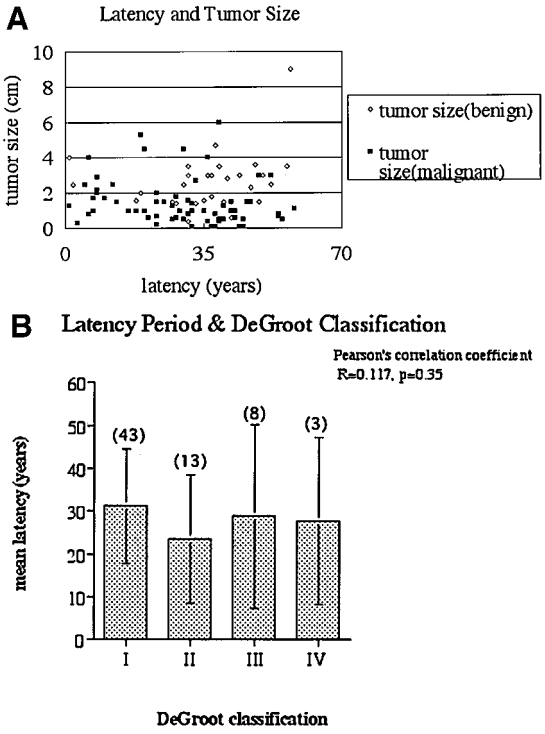

FIGURE 5. Correlation between tumor size, DeGroot classification and latency. A, White diamonds show the maximum diameter of benign thyroid tumors except multinodular goiters and black squares show the maximum diameter of malignant thyroid tumors. B, Each histogram represents the mean ± SD. The number of patient is shown in the parenthesis. Seven patients are unknown because they had surgery at other medical centers. There is no correlation between tumor size or tumor aggressiveness and time till clinical treatment.

to be malignant and that the benign and malignant lesions were of similar size argues against selection bias.

Vogelstein and colleagues established a model of carcinogenesis based on colorectal cancers.[10] This model proposes the sequential progression of colon cancer from normal colonic epithelium to dysplasia, to adenoma and eventually to carcinoma. It has also been suggested that follicular carcinomas may develop from follicular adenomas and that manifest thyroid carcinomas arise from occult papillary carcinomas.[6,11] Exposure to radiation is a known environmental risk factor for thyroid tumors, both in animals and man. Specific ret/ PTC rearrangements (mutations) are associated with papillary thyroid carcinomas and ret/PTC3 rearrangements appear to be associated with a more aggressive behavior and a solid type histologic pattern compared with ret/PTC1 related papillary thyroid carcinomas. p53 mutations are common in anaplastic thyroid carcinomas, but are rare in well differentiated thyroid cancers or in benign tumors.[6,11]

It has been suggested that 2 separate pathways exist for thyroid carcinogenesis.[3,5,11] Wynford-Thomas[5] and Fagin[6] suggested that both papillary and follicular thyroid cancers may develop from benign neoplasms. Our findings that the latency period prior to the detection and treatment of benign thyroid neoplasms was longer than that of malignant thyroid neoplasms among our 171 patients with a documented history of radiation exposure suggests that a multiple hit hypothesis[10] may not be correct. Our finding that follicular carcinomas developed considerably earlier than follicular adenomas, and that manifest papillary thyroid carcinomas developed at about the same times as occult papillary carcinomas is somewhat surprising. Yamashita[12] et al, have reported that only about 2% of occult thyroid cancers progress to clinical thyroid cancer. This may help to explain why the latency period in the development of occult and clinically apparent papillary thyroid cancers were similar.

It has been suggested that in individuals exposed to radiation after the Chernobyl nuclear accident, focal micropapillary hyperplasia may be the precursor for papillary carcinomas.[13] Our data from the 21 patients with occult papillary thyroid cancers and 34 with manifest papillary thyroid cancers (2 patients unknown) fails to support this hypothesis. We found no difference between the latency of manifest papillary thyroid carcinoma and occult papillary thyroid carcinoma, and no difference between the latency of early and advanced stage papillary carcinoma. Schneider et al[14] also reported no significant difference in the latency period prior to development of benign and malignant thyroid tumors after radiation exposure.

More evidence is available supporting the progression of follicular adenomas to follicular carcinomas. Hill et al[15] proposed that the carcinogenic process of follicular cells proceeds through a number of stages. Hard[16] reported that, in animals, increased thyroid-stimulating hormone levels activate the differentiation of the follicular cells. This same process is believed to occur after exposure to irradiation in childhood.[16] Small follicular carcinomas are relatively rare, and occasionally histologic examination identifies a follicular carcinoma arising in a follicular adenoma.[17] We were, therefore, surprised when the latency period prior to the onset of follicular carcinomas was shorter than that for follicular adenomas. Our data argue against a progression from benign to malignant follicular tumors and suggest that adenomas and carcinomas may develop independently and not sequentially.

In evaluating specific outcomes of the Chernobyl nuclear accident, Williams[3] previously reported that the latency period between exposure and development of thyroid cancer was surprisingly short compared with the development of thyroid cancers after exposed to other types of radiation exposure.[3] Our data supports his observation since in our patients exposed to fallout from Chernobyl (n = 6) the average latency period before the development of benign tumors was 8.0 years and for the development of malignant thyroid tumors is 7.2 years. Of interest is that the latency

period prior to the detection of papillary carcinomas was only 6.3 years. Possible alternative explanations for this finding are that there was radiation leakage or other environmental conditions or exposure to carcinogens that occurred near Chernobyl prior to the nuclear accident, or that the population is genetically predisposed to thyroid cancer.[18] It is possible that we have only observed the earliest cases in this subset of irradiated patients and that more individuals will develop thyroid tumors subsequently, thereby lengthening the latency period to that observed after external radiation.

Most patients with radiation-induced thyroid cancers were younger than 20 years when radiated. This is consistent with other reports from Chernobyl related cases, where the risk of developing thyroid cancer after irradiation was 3–10 times higher in children than in adults.[19] It also decreased in children from birth to age 12.[3] Although our data documented that thyroid cancers developed in adults who were younger age (<5 years) at the time of exposure, they also show that most of the Chernobyl patients with benign thyroid tumors were also irradiated at an age younger than 20 years of age. Schneider et al[20] reported that the increased risk associated with young age at exposure remains significant when the analysis uses thyroid-specific doses. The thyroid gland of very young children (<5 years) may be more sensitive to the carcinogenic effect of radiation when compared with older children (>5 years) and adults. Our data did not indicate an association between very young and somewhat older children and the subsequent development of thyroid cancer after radiation, but our numbers are relatively small, and we do not know whether there could be some selection bias. Our data do document that young children after radiation exposure have an increased risk of developing both benign and malignant thyroid tumors.

Other researchers have reported that the development of thyroid cancers after exposure to low dose therapeutic radiation increases for at least the first 3 decades.[21] Some studies suggest that thyroid cancers that develop after medium or high dose radiation occur earlier as observed in the relatively small number of patients in our studies[22] or at the same time as that associated with low dose external radiation.[23,24] Most experts believe that thyroid tumors, especially those that developed prior to 10 years after external radiation, may not be radiation-induced. This statement certainly is not true for all radiation associated thyroid neoplasms since the incidence of thyroid cancer after the Chernobyl nuclear accident increased dramatically within 4 years after exposure.[13]

There are several reports related to thyroid carcinogenesis in animals that support Wynford-Thomas' hypothesis of sequential thyroid cancer carcinogenesis.[25–27] Williams reported that rodent thyroid tumors show a clear stepwise progression associated with both morphologic and oncogene changes after radiation.[25] Other investigators reported carcinogenic progression through a number of stages, including follicular cell hypertrophy, hyperplasia and benign and malignant neoplasms.[15] These reports support Wynford-Thomas' hypothesis of sequential thyroid cancer carcinogenesis in animals. Three decades ago Chaikoff et al[26,27] reported that follicular carcinomas arise from preexisting follicular adenomas, but they also noted that papillary carcinomas were malignant from the time of inception. Our data concur with the latter but not the former observation. Although our observations strongly suggest that benign and malignant thyroid tumors that develop after radiation exposure do so independently and not sequentially, it is possible that benign thyroid tumors may be present but not be clinically detected or that there is more delay by the primary care physicians prior to referral of patients with benign thyroid tumors and a history of radiation exposure. It is also possible that "multiple" mutations occur almost simultaneously and not sequentially. Recent experiments document that in transgenic animals transfected with ret/PTC results in papillary thyroid carcinoma.[28] Other "hits" or mutations do not appear to be required for the develop of these thyroid cancers. Also about 80% of children who have developed papillary thyroid carcinoma have ret/PTC mutations.[29]

In conclusion, our data are consistent with the hypothesis that benign and malignant thyroid tumors arise independently from normal thyroid tissues after radiation exposure. Most occult papillary thyroid cancers do not appear to become manifest papillary thyroid cancers and follicular carcinomas do not appear to arise from follicular adenomas. Both the age at radiation exposure and dose of radiation appear to be important factors in determining the latency period prior to the detection of thyroid neoplasms.

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REFERENCES

1. Mizuno T, Kyoizumi S, Suzuki T, et al. Continued expression of a tissue specific activated oncogene in the early steps of radiation-induced human thyroid carcinogenesis. *Oncogene*. 1997;15:1455–1460.
2. Dobyns BM, Hyrmer BA. The surgical management of benign and malignant thyroid neoplasms in Marshall Islanders exposed to hydrogen bomb fallout. *World J Surg*. 1992;16:126–139; discussion 139–140.
3. Williams D. Thyroid cancer and the Chernobyl accident [editorial] [see comments]. *J Clin Endocrinol Metabol*. 1996;81:6–8.
4. Greenspan FS. Radiation exposure and thyroid cancer. *JAMA*. 1977;237: 2089–2091.
5. Wynford-Thomas D. Origin and progression of thyroid epithelial tumours: cellular and molecular mechanisms. *Hormone Res*. 1997;47:145–157.
6. Fagin JA, Matsuo K, Karmakar A, et al. High prevalence of mutations of the p53 gene in poorly differentiated human thyroid carcinomas. *J Clin Invest*. 1993;91:179–184.
7. Nishiyama RH. Another dissertation on poorly differentiated carcinomas: is it really necessary? *Adv Anatomic Pathol*. 1999;6:281–286.
8. Likhtarev IA, Shandala NK, Gulko GM, et al. Ukrainian thyroid doses after the Chernobyl accident. *Health Phys*. 1993;64:594–599.

9. DeGroot MJ, Stanbury JB. *The Thyroid and its Diseases*. 4th ed. New York: John Wiley & Sons, Inc.; 1975.
10. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell*. 1990;61:759–767.
11. Williams ED. Thyroid tumorigenesis. *Hormone Res*. 1994;42:31–34.
12. Yamashita H, et al. (eds.) *Occult Micro Cancer and Clinical Cancer*. St. Louis: Quality Medical Publishers;. 2000.
13. Nikiforov Y, Gnepp DR, Fagin JA. Thyroid lesions in children and adolescents after the Chernobyl disaster: implications for the study of radiation tumorigenesis [see comments]. *J Clin Endocrinol Metab*. 1996;81:9–14.
14. Schneider AB, Shore-Freedman E, Weinstein RA. Radiation-induced thyroid and other head and neck tumors: occurrence of multiple tumors and analysis of risk factors. *J Clin Endocrinol Metab*. 1986;63:107–112.
15. Hill RN, Erdreich LS, Paynter OE, et al. Thyroid follicular cell carcinogenesis. *Fundam Appl Toxicol*. 1989;12:629–697.
16. Hard GC. Recent developments in the investigation of thyroid regulation and thyroid carcinogenesis. *Environ Health Perspect*. 1998;106:427–436.
17. Williams D. Morphological aspects of thyroid cancer and tumour prognosis. *J Endocrinol Invest*. 1995;18:153–154.
18. Balter M. Chernobyl's thyroid cancer toll [news]. *Science*. 1995;270:1758–1759.
19. Malone J, Unger J, Delange F, et al. Thyroid consequences of Chernobyl accident in the countries of the European Community. *J Endocrinol Invest*. 1991;14:701–717.
20. Schneider AB, Ron E, Lubin J, et al. Dose-response relationships for radiation-induced thyroid cancer and thyroid nodules: evidence for the prolonged effects of radiation on the thyroid. *J Clin Endocrinol Metab*. 1993;77:362–369.
21. DeGroot L, Paloyan E. Thyroid carcinoma and radiation. A Chicago endemic. *JAMA*. 1973;225:487–491.
22. Carr RF, LiVolsi VA. Morphologic changes in the thyroid after irradiation for Hodgkin's and non-Hodgkin's lymphoma. *Cancer*. 1989;64:825–829.
23. Fraker DL. Radiation exposure and other factors that predispose to human thyroid neoplasia. *Surg Clin North Am*. 1995;75:365–375.
24. Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. *N Engl J Med*. 1991;325:599–605.
25. Williams ED. Cell proliferation and thyroid neoplasia. *Toxicol Lett*. 1992;64–65:375–379.
26. Lindsay S, Nichols CWJr, et al. Carcinogenic effect of irradiation. Low doses of radioactive iodine on the thyroid gland of the rat and mouse. *Arch Pathol*. 1968;85:487–492.
27. Lindsay S, Nichols CWJr, Chaikoff IL. Induction of benign and malignant thyroid neoplasms in the rat. Induction of thyroid neoplasms by injection of 131-I with or without the feeding of diets containing propylthiouracil and/or desiccated thyroid. *Arch Pathol*. 1966;81:308–316.
28. Santoro M, Chiappetta G, Cerrato A, et al. Development of thyroid papillary carcinomas secondary to tissue-specific expression of the RET/PTC1 oncogene in transgenic mice. *Oncogene*. 1996;12:1821–1826.
29. Schlumberger M, Cailleux AF, Suarez HG, et al. Irradiation and second cancers. The thyroid as a case in point. Comptes Rendus de L Academie des Sciences. Serie III. *Sci la Vie*. 1999;322:205–213.